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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Yaeta Endo

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER

BRISTOL, LYNN ANNE

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/522,000	Applicant(s) ENDO ET AL.	
	Examiner Lynn Bristol	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 12-16 and 18-28 is/are pending in the application.
- 4a) Of the above claim(s) 12-16, 18, 19 and 25-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 20-24 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/8/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-9, 12-16 and 18-28 are all the pending claims for this application.
2. Claims 12-16, 18, 19 and 25-27 are withdrawn.
3. Claims 1-9, 20-24 and 28 are all the pending claims under examination.
4. Applicants amendments to the claims have necessitated new grounds for rejection. This action in FINAL.

Information Disclosure Statement

5. The IPER document cited in the IDS of 4/8/05 has been considered and entered.

Withdrawal of Objections

Specification

6. The objection to the specification for the figure legend to Figure 1 (p. 14, lines 25-26) for failing to include the sequence identifiers for the two peptide sequences disclosed in Figure 1 is withdrawn.

The amendment to the specification on p. 2 of the Response of 9/11/07 and the revised Sequence Listing to include SEQ ID NOS: 10 and 11 obviates the objection. Applicants' comments on p. 12 of the Response of 9/11/07 are acknowledged.

7. The objection to the specification for the improper use of the trademark, MinisartTM, is withdrawn.

Claim Rejections - 35 USC § 102

10. The rejection of Claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Luo et al. (J. Biotechnol. 65:225-228 (1998); cited in the IDS of 1/18/05 and the PTO 892 form of 3/12/07) is withdrawn.

The amendment of Claims 1 and 2 to recite that the heavy and light chain of the single chain antibody are "directly crosslinked through a linker" and where the linker is bound to a labeling substance overcomes the rejection in view of Luo. Applicants' comments on p. 14 of the Response of 9/11/07 are acknowledged.

11. The rejection of Claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (Cancer Res. 60:6663-6669 (2000)) is withdrawn.

The amendment of Claims 1 and 2 to recite that the heavy and light chain of the single chain antibody are "directly crosslinked through a linker" and where the linker is bound to a labeling substance overcomes the rejection in view of Luo. Applicants' comments on pp. 14-15 of the Response of 9/11/07 are acknowledged.

12. The rejection of Claims 1-8 under 35 U.S.C. 102 (b) as being anticipated by Mascarenhas et al. (USPN 5914254; published June 22, 1999) is withdrawn.

Applicants allege Mascarenhas teaches that the peptide linkers are positioned between the fusion protein and the protein/peptide of interest, where the peptide of interest can be a scFv. Mascarenhas does not teach cross-linking the heavy and light

The amendment to the specification on p. 2 of the Response of 9/11/07 obviates the objection. Applicants' comments on p. 12 of the Response of 9/11/07 are acknowledged.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

8. The rejection of Claims 1, 9, 20-24 and 28 for the recitation that the antibody "carries" or is "carrying" a labeling substance in the linker part is withdrawn for Claims 1, 20-24 and 28.

The amendment of the claims to recite the heavy and light chains are linked through a linker where the linker is bound to a labeling substance overcomes the rejection. Applicants' comments on p.13 of the Response of 9/11/07 are acknowledged.

9. The rejection of Claim 28 for the recitation the antibody "has a Kd value that is equivalent to a Kd value of a naturally occurring antibody" is withdrawn.

The amendment of the claim to recite a parental antibody overcomes the rejection. Applicants' comments on p.13 of the Response of 9/11/07 are acknowledged.

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chain (of the scFv) with a linker, which also binds to a labeling substance (p. 15 of the Response of 9/11/07).

13. The rejection of Claims 1-9, 20-24 and 28 under 35 U.S.C. 102(e) as being anticipated by Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002) is withdrawn.

Applicants allege Fricker teaches that the targeting moiety (anti-idiotypic scFv) is attached to a fluorescent polypeptide and the mimic moiety (anti-idiotypic scFv) is attached to another fluorescent polypeptide, where the two fluorescent peptides are attached. Fricker does not disclose cross-linking the heavy and light chain (of the scFv) with a linker, which also binds to a labeling substance (p. 16-17 of the Response of 9/11/07).

Claim Rejections - 35 USC § 103

14. The rejection of Claims 1-9, 20-24 and 28 under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. (USPN 5914254; published June 22, 1999) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002) is withdrawn.

Applicants allege Mascarenhas does not teach cross-linking the heavy and light chain (of the scFv) with a linker, which also binds to a labeling substance, and where the linker is modified to include His tag labels inserted within the peptide linker.

Applicants allege that none of the reference describe that if the linker moiety of a single

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chain antibody is loaded with a labeling material, it can be labeled without affecting its ability to recognize antigens (pp. 17-19 of the Response of 9/11/07).

Rejections Maintained

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. The rejection of Claims 2-9 for the recitation that the antibody "carries" or is "carrying" a labeling substance in the linker part is maintained.

Applicants have not addressed this aspect of the rejection in their Response of 9/11/07, and therefore the response is incomplete.

16. The rejection of Claim 9 for the recitation the antibody "has a Kd value that is equivalent to a Kd value of a naturally occurring antibody" is maintained.

It is not clear what reference antibody is being compared to. Applicants have not addressed this aspect of the rejection in their Response of 9/11/07, and therefore the response is incomplete.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 3, 4, 7, 8, 20-24 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 3, 4, 7, 8 and 21-24 and 28 are indefinite for the recitation "labeling substance is a substance that is capable of binding to a polypeptide of the linker part of the antibody in the presence of a specific enzyme" in Claims 3, 4, 7, 8 and 21 (elements 3, 4, 7 and 8) because it is not clear what the relationship is between the labeling substance that is bound to the linker and the polypeptide that is part of the linker. It appears that the linker comprises two structural elements:- the labeling substance and a polypeptide that is reactive with the labeling substance. Further, it appears that binding between the labeling substance and the polypeptide requires the presence of an enzyme, and the relationship or function of the enzyme in this binding reaction is not clear.

b) Claim 20 is indefinite for the recitation "wherein DNA is subjected to transcription and translation utilizing a wheat embryo-derived cell-free protein translation system in the presence of a labeling substance and an enzyme that catalyzes a disulfide bond exchange reaction" because it is not clear how the labeling substance and the enzyme that catalyzes a disulfide bond exchange reaction contribute to the

transcription and translation of the DNA in the wheat embryo-derived cell-free protein translation system.

c) Claim 20 is indefinite for the recitation "the DNA encoding the linker comprises a nucleotide sequence that is capable of binding with a labeling substance in the presence of a specific enzyme after translation" because it is not clear how the nucleotide sequence binds the labeling substance in the presence of the enzyme. Alternatively, it is not clear if the phrase "after translation" refers to the DNA encoding the linker, the labeling substance, the specific enzyme or all three.

Priority

18. The priority claim to Applicants parent application PCT/JP03/09140 (filed 7/18/2003) is acknowledged. Applicants have not provided a certified translation of the priority document, JP 2002-210067 (filed 7/18/2002), and therefore the claims are given benefit of the priority filing date of 7/18/2003.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19 Claims 1, 2, 5, 6, 21, 23 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Pavlinkova et al. (Peptides 24:353-362 (March 2003)).

The interpretation of Claims 1, 2, 5, 6, 21, 23 and 24 is of record as set forth in the Office Action of 6/11/07. Claims 1 and 21 have been amended and are now interpreted as being drawn to the single chain antibody having a heavy and light chain being directly crosslinked through a linker where the linker is bound to a labeling substance (Claim 1), and a method for producing the immobilized single chain antibody on a surface which is reacted with a substance that specifically binds the labeling substance where the heavy and light chain are crosslinked through a linker and the linker binds to the labeling substance (element 1) of Claim 21) or the heavy and light chain are variable regions (element 2) of Claim 21) or the labeling substance is incorporated as one part of the linker (element 5) of Claim 21) or the heavy and light chain are variable regions and the labeling substance is incorporated as one part of the linker (element 6) of Claim 21).

Pavlinkova disclose scFv antibodies containing strepavidin-binding peptide or a biotin-like mimic peptide (BMP) where the scFv is modified to contain the BMP. The dimeric scFv comprises VL-linker-VH-linker-VL-linker-VH where the BMP having amino acid sequence SAWRHPQFGG was added to the carboxyl terminus of the VH region by adding the nucleotide sequence shown in figure 1 (Materials and Methods, p. 354, Col. 2, ¶2). One of ordinary skill in the art would reasonably interpret that the addition of the BMP to the C-terminus of the VH domain could occur at either VH domain for the dimeric scFV such as: VL-linker-VH-BMP-linker-VL-linker-VH or VL-linker-VH-BMP-linker-VL-linker-VH-BMP or VL-linker-VH-linker-VL-linker-VH-BMP absent a showing to the contrary. The first and second embodiments of the dimeric scFv would require that

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the labeling substance, BMP, bind to the linker vis-à-vis a fusion as taught by Pavlinkova. Pavlinkova teaches expressing the scFvs in Yeast expression systems, detecting the scFvs by ELISA where the single chain antibody would be immobilized, reacting the scFvs with streptavidin to form a complex. Pavlinkova teaches that another scFv-BMP molecule recognizing CA125, had also been generated by others, thus the insertion of a biotin-like or BMP labeling substance within the linker or binding to the linker vis-à-vis a fusion was already known in the art (p. 359, Col. 1, ¶2) and one could readily envisage the combination of scFv-BMP molecules. Pavlinkova teaches that the immunoreactivity of the single chain antibody was unchanged compared to the parent scFV (p. 359, Col.2, ¶2). Pavlinkova teaches that a labeling substance can block the binding sites or hinder the binding of the conjugate to the targeting moiety, but that insertion of the BMP into a strictly defined site ensures that the immunoreactivity is retained.

It is noted that the labeling substance of the instant invention is not limited to the peptide of SEQ ID NO: 11 as shown in Figure 1 of the instant specification, therefore any biotin peptide or BMP as taught by Pavlinkova anticipates the claimed single chain antibody.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. Claims 1, 9, 21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlinkova et al. (Peptides 24:353-362 (March 2003) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002; cited in the PTO 892 form of 6/11/07).

The interpretation of Claims 1 and 21 is discussed supra. Claims 9 and 21 are interpreted as being drawn to the single chain antibody being produced by a cell-free protein translation system using wheat embryo.

The claimed single chain antibody (Claims 1 and 9) and the claimed immobilized single chain antibody (Claims 21 and 28) being produced by a wheat-embryo derived cell-free translation system was prima facie obvious at the time of the invention over Pavlinkova in view of Fricker.

The interpretation of Pavlinkova is discussed supra. Pavlinkova teaches and appreciates that the engineered construct assures consistency of quality and structure (p. 359, Col. 2, ¶2), but does not disclose production in a wheat-embryo derived cell-free translation system while Fricker does.

Fricker discloses scFV networks comprising an idiotype scFv attached to a first fluorescent polypeptide; and a anti-idiotype scFv which is attached to a second fluorescent polypeptide; and a linker which connects the two fluorescent polypeptides. Fricker discloses producing the probes in cell-free translation systems [0055] including wheat [0158].

One skilled in the art would have been motivated to have produced the instant claimed antibodies and immobilized antibody based on the combined disclosures of Pavlinkova and Fricker. Both Pavlinkova and Fricker explicitly teach single chain antibodies scFvs having peptide linkers or spacers which further comprise or have inserted within or bound to the spacer/linker a labeling molecule such as polyhistidine tag or biotinylation peptide sequence. Both Pavlinkova and Fricker teach immobilization of the scFv in a solid plate. Fricker discloses cell-free translation of the antibodies and expression in wheat. Because Fricker discloses producing a multimeric scFv complex under these conditions, one skilled in the art could have readily modified the scFv of Pavlinkova to have been expressed in a wheat embryo-derived system in order to obtain a homogeneous, exogenous protein free scFv isolate. One could have reasonably expected to have achieved the single chain antibodies because the reagents were available and the techniques for producing single chain antibodies much less the fusion proteins comprising labeling-substance modified scFvs were within ordinary skill of the art at the time of the invention. Each of the references also appreciates the convenience of an internal or linker-associated label which facilitates purification or identification of the single chain antibody or which can be used to easily

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immobilize the antibody by binding of the label to its recognition site. Further because the scFv of Pavlinkova is a simplification of the "idiotype network" of Fricker or seemingly structurally less complex, one would have been further motivated to have combined the references and been assured of success in doing so to produce single chain antibodies and immobilized forms thereof and expressed in wheat embryo translation systems. For all of these reasons, the claims were prima facie obvious at the time of the invention over Pavlinkova and Fricker.

Conclusion

21. No claims are allowed.
22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883.

The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/Larry R. Helms/

Supervisory Patent Examiner